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APPLICATION NUMBER: *60/465,476*
FILING DATE: *April 25, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US04/13034*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

M. Tarver

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04-2803 EL939024325US A1

PTO/SB/16 (10-01)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.	EL 939024325 US

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Gerard M.	Nolan	Farmington, Connecticut

☐ Additional inventors are being named on the _____ separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

Method and Composition for Preventing, Reducing and Reversing Ocular Ischemic Neuronal Damage

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ENCLOSED APPLICATION PARTS (check all that apply)

☑ Specification	Number of Pages: 6	☐ CD(s), Number	
☐ Drawing(s)	Number of Sheets	☐ Other (specify)	
☐ Application Data Sheet. See 37 CFR 1.76			

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

		FILING FEE AMOUNT ($)
☑	Applicant claims small entity status. See 37 CFR 1.27.	
☑	A check or money order is enclosed to cover the filing fees	
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,

SIGNATURE _____ Date 04/25/2003

TYPED or PRINTED NAME Nanda P.B.A. Kumar REGISTRATION NO. (if appropriate) 44,853

TELEPHONE 215-241-7991 Docket Number: 03-40062-USPR

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This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

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TOTAL AMOUNT OF PAYMENT ($) 80.00

Complete if Known	
Application Number	Not yet known
Filing Date	Herewith
First Named Inventor	Nolan
Examiner Name	Not yet known
Art Unit	Not yet known
Attorney Docket No.	03-40062-USPR

METHOD OF PAYMENT *(check all that apply)*

☑ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 18-0586

Deposit Account Name: ReedSmith LLP

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	750	2001	375	Utility filing fee	
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1003	520	2003	260	Plant filing fee	
1004	750	2004	375	Reissue filing fee	
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SUBTOTAL (1) ($) 80.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

		Extra Claims		Fee from below	Fee Paid
Total Claims		-20** =		X	=
Independent Claims		- 3** =		X	=
Multiple Dependent					=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	** Reissue independent claims over original patent
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SUBTOTAL (2) ($)

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

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1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	410	2252	205	Extension for reply within second month	
1253	930	2253	465	Extension for reply within third month	
1254	1,450	2254	725	Extension for reply within fourth month	
1255	1,970	2255	985	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,300	2453	650	Petition to revive - unintentional	
1501	1,300	2501	650	Utility issue fee (or reissue)	
1502	470	2502	235	Design issue fee	
1503	630	2503	315	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	750	2809	375	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	750	2810	375	For each additional invention to be examined (37 CFR 1.129(b))	
1801	750	2801	375	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

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SUBMITTED BY				(Complete *if applicable*)	
Name (Print/Type)	Nanda P.B.A. Kumar	*Registration No. (Attorney/Agent)*	44,853	*Telephone*	215-241-7991
Signature				*Date*	April 25, 2003

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EXPRESS MAIL CERTIFICATE (37 CFR 1.10)

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Date of Deposit April 25, 2003

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Name: Franziska Reichstein

Signature Franziska Reichstein

April 25, 2003

Box Provisional Patent Application
Commissioner for Patents
Washington, D.C. 20231

RE: New Provisional Patent Application
Applicant: Nolan
Filing Date: herewith
For: Method and Composition for Preventing, Reducing and Reversing Ocular Ischemic Neuronal Damage
Docket No. 03-40062-US (939024.20009)

Dear Sir:

Enclosed are the following for filing in connection with the above-referenced application:

1. Provisional Application For Patent Cover Sheet;
2. Fee Transmittal for FY 2003;
3. A check in the amount of $80.00 to cover the filing fee for a provisional application;
4. Application consisting of 6 pages of specification, 3 pages of claims, and 1 page of abstract; and
5. A self-addressed stamped postcard, return of which is requested to acknowledge receipt of the enclosed documents.

2500 One Liberty Place
1650 Market Street
Philadelphia, PA 19103-7301
215.851.8100
Fax 215.851.1420

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The Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account No. 18-0586.

Respectfully submitted,

Nanda P.B.A. Kumar
Registration No. 44,853

NPK/fr
Enclosures

DOCKET NO.: 03-40062-USPR

In the United States Patent and Trademark Office

UTILITY PATENT APPLICATION

TITLE: Method and Composition for Preventing, Reducing and Reversing Ocular Ischemic Neuronal Damage.

INVENTORS:

Dr. Gerard M. Nolan
231 Farmington Avenue
Farmington, CT 06032

Method and composition for preventing, reducing and reversing ocular ischemic neuronal damage.

FIELD OF THE INVENTION

The present invention relates to a newly identified method and composition for treating and preventing ischemic ocular neuronal damage with a weekly administration of an acetylcholinesterase inhibitor. Specifically, the invention provides method and composition for treatment and prevention of congenital and acquired ischemic conditions which threaten the nerves of the visual system of mammals; these conditions include but are not limited to: macular degeneration, retinitis pigmentosa, optic neuritis, neuroretinitis, Lebers congenital amaurosis, Stargardts disease, Parkinson's disease, diabetic retinopathy, idiopathic senile vision loss, uveitis, edema and ocular surgery.

BACKGROUND OF THE INVENTION

The health of a mammalian visual system is dependent upon the proper vascular perfusion of all constituent eye components, including: the retina, macula, choroid, sclera, ciliary body, conjunctiva and optic nerve. Afferent and efferent blood flow is critical to supplying nutrients, maintaining osmotic balances and removing waste products. The mammalian eye is vulnerable to many congenital and acquired focal ischemic conditions which can deprive the visual system of proper blood supply. Focal ischemia occurs under conditions in which a portion of the visual system is deprived of its normal blood supply, such as may result from choroidal neovascularization, the formation of drusen, reductions in ciliary activity, uveitis, edema, ocular surgery, traumatic injury, or visual pathway tumors.

Focal ischemic conditions have the potential for producing widespread neuronal damage, even if the ischemic condition is transient. Much of this neuronal damage is attributed to secondary consequences of reperfusion of the tissue, such as the release of vasoactive products by damaged endothelium, and the release of cytotoxic products (free radicals, leukotrienes, etc.) by damaged tissues.

Acetylcholine (ACh) has been determined to be a key regulatory agent in visual system perfusion. AChdeficiencies are known to result in reduced capillary constriction and sharp decreases in ocular blood flow.

SUMMARY OF THE INVENTION

The present invention provides a method of preventing, reducing and reversing ocular neuronal damage related to various ischemic conditions affecting the visual system of a mammal. In this method, an amount of a acetylcholine esterase inhibitor is administered

to one or both eyes of the mammal affected by or vulnerable to ischemic ocular neuronal damage, such that it provides a therapeutic benefit. Specifically, the inhibitor causes increased ciliary activity, trabecular flow and choroidal perfusion within the mammalian eye. Also forming part of the invention is a method of reducing neuronal damage related to an ischemic condition. Increased amplification of visual system neuronal signals to the mammalian occipital lobe is also provided.

DETAILED DESCRIPTION OF THE INVENTION

For decades, it has been demonstrated that within the mammalian visual nervous system, a phenomenon known as neuronal cell death takes place. This cell death is regulated by the release of neurotrophins. Neurotrophins are a family of small polypeptides which bind to low affinity receptors throughout the visual system[15]

Acetylcholine (ACh) was the first neurotransmitter to be identified[5] and its effects on synaptic neuromuscular transmission are well established. It has been shown that ACh is involved in many higher-level neuronal events such as cognition, memory and plasticity.[8] Further, it has recently been shown that an enhancement in ACh activity reduces neural cell death[17] and the death of related Purkinje cells.[11]

The release of neurotrophins by neuronal cells can be stimulated either by depolarization or by glutamate.[1,10] An important role of cholinergic (ACh) activity on the synthesis and release of trophic molecules by glial cells has been demonstrated in different regions of the CNS.[3,13] Interactions between neuronal and glial cells play a fundamental role in the adult nervous system.[9,17] Moreover, the role of glial cells protecting neuronal cells from excitotoxicity depends on neuron–glial interactions, as mediated by ACh.[16]

The role of cholinergic activity in the differentiation and survival of retinal neurons is not well understood. It has been previously demonstrated that treatment with veratridine increases the survival of retinal ganglion cells. This effect was blocked by atropine indicating the importance of cholinergic activity on neuronal survival.[15] Within the inner plexiform layer of the retina, muscarinic receptors have been identified on processes from all three inner retinal neuron types; in the outer plexiform layer, muscarinic receptors are critical to the functioning of second-order cells, with highest densities along the bipolar dendrites.

Pereira and Araujo (2002) show that in-vitro carbamycholine induces a two-fold increase in retinal ganglion cell survival, through the activation of M_1 receptors, they concluded that muscarinic activity controls the survival of retinal ganglion cells via a release of polypeptides.[14]

The healthy activity level of afferent cells such as rods and cones within the retina also plays an important role in regulating neuronal cell death. The blockade of electrical activity of afferent cells such as these will, in itself, induce neuronal degeneration within target cells.[15]

Systemic ACh levels within the eye often serves to limit the action of ACh within visual information processing.[2]

Niemeyer, et al. explored the impact of applying a muscarinic antagonist (Quinuclidinyl benzilate) to block of retinal cholinergic reception. They observed a dose-related decrease in retinal perfusion, suggesting a substantial contribution of muscarinic cholinergic transmission toward retinal viability.[12]

Fischer, et al. identified three different muscarinic receptors (cm2, cm3, cm4) within the eye and mapped each receptor type for its geographic distribution and unique function.[6]

It is likely that ACh release within the eye mediates the interactions between retinal cells and ION terminals which innervate the inferior retina and are thought to be essential in the enhancement of visual responses communicated by retinal ganglion cells.[4]

A separate observation suggests a vasoactive role for ACh. Wu, et al. studied the presence of muscarinic receptors on pericytes, which are abluminally positioned contractile cells that regulate capillary perfusion. Wu found that the activation of (Ach) muscarinic receptors elevated pericyte calcium levels, increased depolarizing calcium-activated chloride currents and caused pericytes to contract. Most contracting pericytes were near capillary bifurcations, causing capillary lumens to constrict. The result of higher muscarinic stimulation was increased capillary perfusion to the retina.[18]

Franklin and Johnson lend support to this theory of ACh-dependent longevity; they found that prolonged and frequent depolarization of neurons led to an increase in cytoplasmic free Ca2+, which served to suppress programmed cell death and promote neuronal survival.[7]

This invention utilizes the application of an ophthalmic acetylcholinesterase inhibitor, or pharmaceutical equivalent thereof, to increase ocular ACh availability and thereby heighten muscarinic activity, ganglionic signal and retinal perfusion. There is miosis dilate. Cycloplege paralysis of vision has no effect on first day, but accelerated decline on days 4&5

The present treatment provides amplification of synaptic transmissions through its enhancement of retinal muscarinic receptor functionality, thereby improving the quality of information destined for the occipital lobe of the brain. Specifically, our unexpected success in reversing CNS-based visual loss related to amblyopia, optic neuritis and Parkinson's disease has been disclosed.

Furthermore, a muscarinic basis to present effect is proven here, through the induction of cycloplegic paralysis (using cyclopentolate). If induced on the morning immediately following treatment with low-dose echothiophate, one can observe no loss of subject vision gains, but if induced at day 4-5, there is significant, premature reversal of the effect.

Choroidal circulation and retinal perfusion are visibly increased, within the effects of low-dose echothiophate. This is supported by before and after fluorescent angiograms

performed across trial subjects. Additionally, increased ciliary body activity increases blood flow to and from the choroid.

Despite the many obvious anterior eye benefits of low-dose echothiophate, including a strengthening of accommodation and ciliary enhancement, there is overwhelming evidence that the primary therapeutic benefits lie within the retinal neuronal network.

Ophthalmic compositions comprising acetylcholinesterase inhibitors are known, in the art, and commercially available, e.g. under the trade name Phospholine Iodide. However, it has been found that these compositions do not exhibit the above therapeutic effects.

Further, these existing compositions typically have to be applied two to three times a day. It has been found that such repeated administration is not optimal in practice, because, inter alia, for optimal treatment the patient has to have the medicament always available and the patient is disturbed several times a day. Such multiple administration of a drug, in particular of an ophthalmic composition, leads generally to the problem of overdosing and underdosing.

Surprisingly, it has now been found that an ophthalmic acetylcholinesterase inhibitor such as Phospholine Iodide can be formulated for weekly administration which weekly administration provides therapeutic efficacy in the eye over about 7 days and that such compositions are surprisingly well tolerated. Moreover the abovementioned weekly ophthalmic compositions produce a highly reliable and more beneficial clinical result in a patient treated therewith.

Therefore, in one aspect the present invention provides an ophthalmic composition suitable for weekly administration to the eye before sleep, comprising an ophthalmic anticholinesterase inhibitor from about 0.001-0.25%. Preferred inhibitor is (2-mercaptoethyl) trimethylammonium iodide O,O-diethyl phosphorothioate. Preferred concentrations of the inhibitor is 0.001%, 0.015% and 0.03%.

The compostions of the present invention comprise an active ingredient at a concentration so that an effective amount thereof is contained in a drop, wherein said drop amounts about 10-100 µl (microliters), preferably about 20-70 µl, and especially about 25-50 µl.

Mammals in the present invention include not only humans but also other animals selected from a group consisting of mice, rats, rabbits, pigs, cows, goats, dogs, cats and monkeys.

All publication references, patents and patent applications mentioned in this specification are indicative of the level of those skilled in the art to which this invention pertains. The contents of all the publications, patents and patent applications are herein incorporated by reference to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

References

[1] Abiru, Y., Katoh-Semba, R., Nishio, C., Hatanaka, H., 1998. High potassium enhances secretion of neurotrophic factors from cultured astrocytes. Brain Res. 809, 115–126.

[2] Beelke M., Sannita W.G. Cholinergic function and dysfunction in the visual system. Methods Find Exp. Clin. Pharmacol. 24 Suppl D (2002) 113-117.

[3] Berzaghi, M.P., Cooper, J., Castren, E., Zafra, F., Sofroniew, M., Thoenen, H., Lindholn, D., 1993. Cholinergic regulation of brainderived neurotrophic factor (BDNF) and nerve growth factor (NGF) but not neurotrophin -3 (NT-3) mRNA levels in the developing rat hippocampus. J. Neurosci. 13, 3818–3826.

[4] Calaza K.C., Gardino P.F. Evidence of muscarinic acetylcholine receptors in the retinal centrifugal system of the chick. Brazillian J. Med & Biol Res. (200) 33: 1075-1082.

[5] Dale, H.H., Felberg, W., Vogt, M., 1936. Release of acetylcholine at voluntary motor nerve endings. J. Physiol. Lond. 82, 121–128.

[6] Fischer A., McKinnon L, Nathanson N, Stell W. Identification and localization of muscarinic acetylcholine receptors in the ocular tissues of the chick. J. Comp. Neurology. 392: 273-284.

[7]

[8] Hohmann, C.F., Berger-Sweeney, J., 1998. Cholinergic regulation of cortical development and plasticity. Perspect. Dev. Neurobiol. 5, 401–425.

[9] Hulme, E.C., Curtis, C.A.M., Page, K.M., Jones, P.G., 1993. Agonist activation of muscarinic acetylcholine receptors. Cell. Signal. 3, 687–694.

[10] Kuhn, W., Mu¨ ller, T.H., 1995. Exogenous stimulation of NGF synthesis by catecholamines and their analogues. J. Neural Transm. 46, 189–192.

[11] Mount, H.T.J., Dreyfus, C.F., Black, I.B., 1994. Muscarinic stimulation promotes cultured Purkinje cell survival: a role for acetylcholine in cerebellar developmental? J. Neurochem. 63, 2065–2073.

[12] Niemeyer G., Jurklies B., Kaelin-Lang A., Bittiger H. Binding and electrophysiology of the muscarinic antagonist QNB in the mammalian retina. Klin Monatsbl Augenheilkd. May, 1995. 206 (5): 380-383.

[13] O'Malley, D.M., Sandell, J.H., Masland, R.H., 1992. Co-release of acetylcholine and GABA by the starburst amacrine. J. Neurosci. 12 (4), 1394–1408.

[14] Pereira, S.P.F., Araujo, E.G., 2000. Chronic Depolarization induced by veratridine increases the survival of rat retinal ganglion cells after 48 hours 'in vitro'. Int. J. Dev. Neurosci. 18, 773–780.

[15] Pereira S.P.F., Medina S.V., Araujo E.G. Cholinergic activity modulates the survival of retinal ganglion cells in culture: the role of M1 muscarinic receptors. I.J. Developmental Neuroscience. 19 (2001) 559-567.

[16] Raju, T.R., Bennett, M.R., 1986. Retinal ganglion cells survival requirements: a major but transient dependence on Muller glia during development. Brain Res. 383, 165–176.

[17] Rinner, J., Kukulanky, T., Flesner, P., Skreiner, E., Globerson, A., Kasai, M., Hirokawa, K., Korsako, W., Schauenstein, K., 1994. Cholinergic stimulation modulates apoptosis and differentiation of murine thymocytes via A nicotinic effect on thymic epthelium. Biochem. Biophys. Res. Com. 203, 1057–1062.

[18] Wu, D.M., Kawamura W.D., Sakagami K., Kobayashi M., Puro D.G. Cholinergic regulation of pericyte-containing retinal microvessels. Am. J. Physiol Heart Circ Physiol. Jan, 2003.

Table One: Examples of visual acuity improvements within low-dose echothiophate subjects..

Subject Initials	Sex	Condition	Dosage	Distant Vision		Near Vision (Jaeger)		Color Vision (Ishihara)	
				Pre-ECHO	Post-ECHO	Pre-ECHO	Post-ECHO	Pre-ECHO	Post-ECHO
BB[2]	F	*Amblyopia*	0.010	20/200	20/200	18	16^{-1+1}	0	5
NM	M	*Amblyopia*	0.015	20/70	$20/50^{+2}$	1	1	10	10
WD[2]	F	*Amblyopia*	0.010	$20/50^{-2+3}$	$20/30^{-2}$	7	2	10	10
DK	M	*Brain Tumor*	0.015	20/70	$20/70^{+2}$	3	1^{+}	8	10
BB	F	*Cerebral Stroke*	0.015	20/50	$20/40^{-1}$	7^{-}	2^{-1}	1	1
BH	M	*Central Serous Chorioretinopathy*	0.015	20/300	$20/70^{-}$	16	1^{-2}	2	8
AV	M	*Diab. Retinopathy*	0.015	20/70	$20/30^{-1}$	7^{+}	3^{+}	*N/A*	*N/A*
BR	F	*Diab. Retinopathy*	0.010	20/1600	20/1600	18	18^{-1}	0	0
EM	M	*Diab. Retinopathy*	0.010	$20/25^{-}$	$20/20^{-}$	1^{-1}	1	10	10
TY	M	*Diab. Retinopathy*	0.010	$20/50^{-}$	$20/50^{+}$	16	16	*N/A*	*N/A*
CO	F	*Macular Hole*	0.015	$20/100^{-}$	$20/70^{-1}$	16	3^{-}	*N/A*	*N/A*
TO	M	*Macular Hole*	0.015	20/1600	20/200	18^{+}	10	*N/A*	*N/A*
KC	F	*Migraine/Amblyopia*	0.015	20/8000	20/1600	100	54	2	8
JJ	F	*Optic Neuritis*	0.015	$20/100^{-}$	$20/25^{+}$	5	1^{+}	10	10
MM	M	*Optic Neuritis*	0.015	20/40	$20/25^{+}$	3^{-}	1	0	0
HN	M	*Parkinson's*	0.015	20/40	$20/20^{+2}$	3	1	10	10
BC	F	*Photocoagulation*	0.010	20/70+2	20/70+3	5-1	3-2	7	8
PB	M	*Photocoagulation*	0.010	20/40	20/25	2+	1+ -1	10	10
RD2	M	*Photocoagulation*	0.015	20/1600	20/400	20	18	0	0
VC	F	*Photocoagulation*	0.010	20/2667	20/400	20/800	16	0	1
CR	F	*Preretinal Fibrosis*	0.015	$20/30^{-1}$	$20/25^{+1}$	1^{-1}	1^{-}	10	10
TL	M	*Retinal Detachment*	0.010	$20/25^{-}$	$20/20^{-1}$	5^{-}	5	10	10
VD	F	*Retinal Hole*	0.015	20/100	$20/100^{++}$	16	3^{+2}	10	10
SB	F	*Retinal Vein Occlusion*	0.010	20/1600	20/1000	16	16^{+}	2	8
KH[2]	F	*Retinitis Pigmentosa*	0.015	20/400	$20/70^{-1}$	7^{-}	2	0	*N/A*
ED	M	*Retinitis Pigmentosa*	0.015	20//8000	20/70	16	7	0	8
RH[2]	M	*Retinitis Pigmentosa*	0.015	20/4000	20/2000	16	10	0	0
VD[2]	M	*Retinitis Pigmentosa*	0.015	$20/30^{-3}$	$20/25^{+4-2}$	7	1^{+}	5	8.5
SL	M	*Solar Retinopathy*	0.010	$20/30^{-1}$	20/25	*N/A*	*N/A*	*N/A*	*N/A*
AF	F	*Stargardts*	0.015	20/1600	20/200	5"/J2	1	0	10
AG	M	*Stargardts*	0.015	20/300	$20/100^{-1}$	10	1^{-}	7	10
GP	M	*Stargardts*	0.015	20/300	20/400	3"/J2	6"/J2	*N/A*	*N/A*
KH	F	*Stargardts*	0.015	$20/200^{+1}$	$20/100^{-1+3}$	5^{-}	1	10	10

WHAT IS CLAIMED IS:

1. A method of preventing, reducing and reversing ocular neuronal damage related to various ischemic conditions affecting the visual system of a mammal, comprising: administration to one or both eyes of a mammal affected by or vulnerable to ischemic ocular neuronal damage, an amount of a acetylcholine esterase inhibitor containing composition sufficient to provide a therapeutic benefit.

2. The method of claim 1, wherein the composition is administered immediately prior to sleep.

3. The method of claim 2, wherein said inhibitor is (2-mercaptoethyl) trimethylammonium iodide O,O-diethyl phosphorothioate.

4. The method of claim 3, wherein said (2-mercaptoethyl) trimethylammonium iodide O,O-diethyl phosphorothioate is present at a concentration of 0.001% to 0.25%.

8. The method of claim 2, wherein the acetylcholine esterase inhibitor is contained in a pharmaceutically acceptable buffer medium.

9. The method of claim 1, wherein the ocular neuronal damage relates to macular degeneration.

10. The method of claim 1, wherein the ocular neuronal damage relates to retinitis pigmentosa.

11. The method of claim 1, wherein the ocular neuronal damage relates to optic neuritis, optic neuropathy and generalized optic nerve ischemia.

12. The method of claim 1, wherein the ocular neuronal damage relates to neuroretinitis.

13. The method of claim 1, wherein the ocular neuronal damage relates to Lebers congenital amaurosis.

14. The method of claim 1, wherein the ocular neuronal damage relates to Stargardts disease.

15. The method of claim 1, wherein the ocular neuronal damage relates to Parkinson's disease.

16. The method of claim 1, wherein the ocular neuronal damage relates to diabetic retinopathy.

17. The method of claim 1, wherein the ocular neuronal damage relates to idiopathic senile vision loss.

18. The method of claim 1, wherein the ocular neuronal damage relates to uveitis.

19. The method of claim 1, wherein the ocular neuronal damage relates to edema.

20. The method of claim 1, wherein the ocular neuronal damage relates to ocular surgery.

21. The method of claim 1, wherein the ocular neuronal damage relates to a thromboembolic event in the retinal vasculature.

22. The method of claim 1, wherein the ocular neuronal damage relates to a visual scotoma.

23. The method of claim 1, wherein the ocular neuronal damage relates to a retinal migraine, ophthalmoplegic migraine or scintillating scotoma.

24. The method of claim 1, wherein the ocular neuronal damage relates to central retinal artery/vein occlusion.

25. The method of claim 1, wherein the ocular neuronal damage relates to branch retinal artery/vein occlusion.

26. The method of claim 1, wherein the ocular neuronal damage relates to anterior ischemic optic neuropathy.

27. The method of claim 1, wherein the ocular neuronal damage relates to giant cell arteritis.

28. The method of claim 1, wherein the ocular neuronal damage relates to retinal hemorrhage.

29. The method of claim 1, wherein the ocular neuronal damage relates to cystoid macular edema.

30. The method of claim 1, wherein the ocular neuronal damage relates to macular cystic degeneration.

31. The method of claim 1, wherein the ocular neuronal damage relates to preretinal fibrosis.

32. The method of claim 1, wherein the ocular neuronal damage relates to ischemic maculopathy.

33. The method of claim 1, wherein the ocular neuronal damage relates to macular holes and cysts.

34. The method of claim 1, wherein the ocular neuronal damage relates to macular epithelial fibrosis.

35. The method of claim 1, wherein the ocular neuronal damage relates to peripapillary staphyloma and peripapillary atrophy.

36. The method of claim 1, wherein the ocular neuronal damage relates to acute macular neuroretinopathy.

37. The method of claim 1, wherein the ocular neuronal damage relates to Plaquenil-related toxicity.

38. An ophthalmic composition for weekly administration to the eye, comprising an acetylcholinesterase inhibitor in an ophthalmic buffer solution.

39. The composition of claim 38, wherein the composition is administered once weekly, immediately prior to sleep.

40. The composition of claim 39, wherein said inhibitor is (2-mercaptoethyl) trimethylammonium iodide O,O-diethyl phosphorothioate.

41. The composition of claim 39, wherein said (2-mercaptoethyl) trimethylammonium iodide O,O-diethyl phosphorothioate is present in said composition at a concentration between about 0.001% and about 0.25%

42. The method of claim 39, wherein the acetylcholine esterase inhibitor is contained in a pharmaceutically acceptable buffer medium.

Abstract

Methods and compositions are provided for preventing, reducing and reversing ischemic neuronal damage related to congenital and acquired ophthalmologic conditions such as macular degeneration, retinitis pigmentosa, optic neuritis, neuroretinitis, Lebers congenital amaurosis, Stargardts disease, Parkinson's disease, diabetic retinopathy, idiopathic senile vision loss, uveitis, edema and ocular surgery. An amount of an acetylcholine esterase inhibitor containing composition may be administered to the eye of a mammal, either topically or via a controlled-release drug delivery system.

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